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Pharmaceuticals Inc.

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

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**Docket No. 96D-0009, International Conference on Harmonisation; Q3B(R) Draft Revised Guidance for Impurities in New Drug Products**

**Comments submitted electronically via e-mail 9/18/00, to fdadockets@oc.fda.gov**

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Dear Sir or Madam:

Boehringer Ingelheim Pharmaceuticals, Inc. wishes to provide the following comments on the subject draft revised ICH Guideline. For convenience, our comments are placed under the section titles of the draft revised Guideline.

In addition to comments on the ICH Q3B(R) Guideline, we would like to take this opportunity to voice our concern over FDA Guidances which are inconsistent with, or contrary to, the ICH Q3B(R) Guideline. Therefore, following our comments on the ICH Q3B(R) Guideline, we have provided comments on inconsistencies between this ICH Guideline and certain FDA draft Guidances for Industry.

**Section 2.2 Rationale for Reporting and Control of Impurities**

The last sentence in this section reads "Conventional rounding rules should be applied and the results presented with the same number of decimals as given in the limit." In order to be unambiguous concerning the rounding rules, please add "refer to Glossary definition of rounding" to this sentence. The sentence should read, "Conventional rounding rules (**refer to Glossary definition of 'Rounding'**) should be applied and the results presented with the same number of decimals as given in the limit."

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Please also add a statement that the rounding of results, per the Glossary definition, may be applied in determining whether or not a threshold has been exceeded. Furthermore, for purposes of such determination, the ICH Guidance should make clear that the number of significant figures in the threshold should be applied, *e.g.*, a result of 1.4% may be rounded to 1% since the thresholds (expressed as a percent) contain one significant figure.

**Section 2.3 Reporting Impurity Content of Batches**

➢ Reporting Threshold

The second sentence of this section contains the term "reporting level", whereas elsewhere in this guideline, the term "reporting threshold" is used. We would like to point out that the term "reporting level' is also used in section 3 on "Range" in ICH Guideline Q2B *Validation of Analytical Procedures: Methodology*.

We suggest that the term "reporting threshold" be used consistently throughout this Q3B guidance, and propose the following changes:

- Change the second sentence of this section to read, "Because the degradation test procedure can be an important support tool for monitoring the manufacturing quality as well as for deciding the expiration dating period of the product, the **reporting threshold** should be set below the identification threshold."

- Assuming there is no difference in the terms "reporting threshold" and "reporting level, change the Glossary definition in section 3 of this guidance to add a second sentence, so that the definition reads "Reporting Threshold: A limit above which an impurity needs to be reported. **The reporting threshold is the same as the reporting level.**"

**Section 2.4 Specification Limits for Degradation Products**

➢ Specified and Unspecified Degradation Products

No guidance has been offered concerning the threshold beyond which an individual degradation product should be "specified", i.e., individually listed and limited in the drug product specifications. This is in contrast to the guidance provided in ICH Q3A(R) *Impurities in New Drug Substances*, where it is stated that individual impurities should be "specified" if "estimated to be present at a level greater than (>) the qualification/identification threshold" [ref: Section 6, ICH Q3A(R)].

Similarly, no guidance is given on the specification limit for "Any unspecified degradation product". This is in contrast to the guidance provided in ICH Q3A(R) *Impurities in New Drug*

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*Substances*, where it is stated that the specifications should include a "general specification limit of not more than the qualification/identification threshold for any unspecified impurity".

We feel that guidance on these points is needed, and we request that the ICH Q3B(R) Guideline state the thresholds over which individual degradation products must be "specified", and also state the recommended specification limit for "individual unspecified degradation product". Since the identification and qualification thresholds differ for drugs dosed in the range of 1 mg – 100 mg per day (Total Daily Dose), the ICH Q3B(R) Guideline should be explicit as to whether the identification or qualification threshold should be used for specifying individual degradation products.

➢ Total Degradation Products

The guideline recommends that the specifications for the product include a limit for "Total degradation products". In addition, the guideline states that "All impurities at a level great than (>) the reporting threshold should be summed and reported as Total Impurities". The latter sentence is inconsistent with the specification, since the definition of "impurity" includes both impurities arising from the synthesis of the drug substance as well as degradation products. Please revise the sentence to read "All **degradation products** at a level greater than (>) the reporting threshold should be summed and reported as "**Total Degradation Products**".

This change would be consistent with section 1.3 Scope of the Q3B(R) Guideline, where it is stated that "Impurities present in the new drug substance need not be monitored or specified in drug products unless they are also degradation products (see ICH Q6A guideline specifications)". This is also consistent with the guidance in the ICH Q6A Guideline, *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*. The ICH Q6A Guideline states in section 3.2.2 d), "Acceptance limits should be stated for individual specified degradation products, which may include both identified and unidentified degradation products as appropriate, and total degradation products". Process impurities from the new drug substance synthesis are normally controlled during drug substance testing, and therefore are not included in the total impurities [sic] limit".

Concerning the calculation of the "Total", the guideline states that "The summation is performed on the unrounded, individual values and the total value is rounded and reported as described in section 2.2". In many cases the individual values are not raw data. Calculations are performed based on the raw data and as a consequence, these individual values are rounded values too. The term "unrounded values" should be replaced. For example: "The summation is performed on **individual values with an appropriate number of significant places for monitoring and evaluating the stability of the drug product**..."

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## ATTACHMENT 1

The second footnote reads "Threshold is based on percent of the substance. Higher reporting thresholds should be scientifically justified.". Please remove the word "reporting" from the second sentence so that it reads "**Higher thresholds should be scientifically justified**". This change makes the second footnote applicable to all thresholds where it is noted. However, if this alters the desired meaning of the footnote, then please remove the use of the footnote (2) against the thresholds for identification and qualification.

## Inconsistency with FDA Guidances for Industry

There is inconsistency between the draft ICH Q3B(R) Guideline and certain FDA draft Guidances, with respect to the requirements for reporting thresholds and specifications for degradation products in drug products.. This raises concern about the status of the ICH Guidelines within FDA.

In the recent draft FDA Guidance for Industry, *Analytical Procedures and Methods Validation*, it is stated that the "total organic impurities for the drug product or drug substance is the sum of all impurities equal to or greater than their individual QL" (Ref: Lines 332-333, Section J. Reporting of Results). The Quantitation Limits of modern analytical procedures are often lower (sometimes much lower) than the ICH reporting thresholds defined in ICH Q3B(R). The proposed FDA requirement to report at or above the Quantitation Limit of an analytical procedure, is inconsistent with the ICH Q3B(R) reporting thresholds.

The draft FDA Guidance for Industry, *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products*, contains a requirement to specify those "Individual impurities or degradation products appearing at levels 0.10 percent or greater" (Ref: Section F.b Specifications for the Drug Product - Impurities and Degradation Products). As noted above, this ICH Q3B(R) Guideline and the ICH Q6A Guideline set forth the concept that "impurities present in the new drug substance need not be monitored or specified in drug products unless they are also degradation products". The FDA guidance requirement to specify "individual impurities" is contrary to the agreed ICH principle that synthetic impurities need not be specified in the drug product specifications. Further, the FDA requirement to specify "degradation products" appearing at levels of 0.10 percent, is inconsistent with the ICH thresholds based on Maximum Daily Dose; the 0.10% level is lower than any identification/qualification threshold listed in the ICH Q3B(R) Guideline.

We would like to emphasize that the harmonization of regulatory requirements for the reporting of impurities and degradation products, and the setting of specifications based on the reported data, is critical to achieving the goal of harmonized content under the ICH M4 Guideline: *The Common Technical Document*. Applicants will never be able to write a single document which is suitable for submission in all three ICH regions in the absence of such fundamental harmonized requirements on this topic. Therefore, FDA's publication of draft guidance which is contrary to the ICH principles is of great concern.

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In closing, we wish to thank FDA for the opportunity to comment on this draft revised ICH Q3B(R) Guideline. Please contact the undersigned with any questions or comments on this correspondence.

Sincerely,

Patricia Watson

Patricia Watson
DRA Technical Director
Drug Regulatory Affairs